form of the target protein that responds to a particular drug, including the active site, has been structurally characterized;

generating a 3-D structural model of the mutated protein;

comparing the structure of the mutated protein with the form of the protein that responds to the drug to identify structural differences and/or similarities arising from the mutations;

comparing the biological activities of the drug against both the mutated protein and the form of the protein that responds to the drug to determine the effects of the mutations on drug response; and

identifying the mutations in the protein that affect biological activity based on the comparisons.

REMARKS

A check for excess claims accompanies this Preliminary Amendment. Any fees that may be due in connection with filing this paper, or during the entire pendency of this application, may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 11, 12, 19-21, 25, 27, 28 and 30 are amended to correct minor obvious grammatical error and minor language inconsistencies. Claims 67-93, which find basis in the specification as originally filed and in the parent application, are added herein. These claims are added to more particularly point out and distinctly claim subject matter that applicant regards as an invention. No new matter is added.

Included, per 37 C.F.R. § 1.121., as an attachment, is a marked-up version of the claims that are amended.

* * *

Entry of this amendment and examination of the application are respectfully requested.

Respectfully submitted,
HELLER, EHRMAN, WHITE & McAULIFFE LLP

By: _____
Stephanie L. Seidman
Registration No. 33,779

Attorney Docket No. 24737-1906C
Address all correspondence to:
Stephanie L. Seidman, Esq.
HELLER EHRMAN WHITE & McAULIFFE LLP
4250 Executive Square, 7th Floor
La Jolla, California 92037-9103
Telephone: (858) 450-8400
Facsimile: (858) 587-5360
EMAIL: sseidman@hewm.com

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Ramnarayan *et al.*

Serial No. 09/709,905

Filed: November 10, 2000

For: USE OF COMPUTATIONALLY DERIVED PROTEIN STRUCTURES OF GENETIC POLYMORPHISMS IN PHARMACOGENOMICS FOR DRUG DESIGN AND CLINICAL APPLICATIONS

Art Unit: Unassigned

Examiner: Unassigned

I hereby certify that this paper and the attached papers are being deposited with the United States Postal Service as first class mail in an envelope addressed to:
Commissioner for Patents
Washington, D.C. 20231, on this date.

04/13/01
Date Stephanie Seidman

ATTACHMENT TO THE PRELIMINARY AMENDMENT MARKED UP PARAGRAPHS AND CLAIMS (37 C.F.R. §1.121)

Please amend claims 11, 12, 19-21, 25, 27, 28 and 30 as follows:

11. (Amended) The method of claim 1, wherein the selected model structures represent the structural variants resulting from genetic polymorphisms found in a selected [patient] subpopulation.

12. (Amended) The method of claim 1, wherein the structural variant models are stored in a relational database, comprising:

3-D molecular coordinates for the structural variants;

a molecular graphics interface for 3-D molecular structure visualization; computer functionality for protein sequence and structural analyses; and

database searching tools.

19. (Amended) The method of claim 17, wherein the selected model structures represent the structural variants resulting from genetic polymorphisms found in a [specific patient] subpopulation.

20. (Twice Amended) The method of claim 12, wherein the selected model structures represent structural variants derived from [patients that] subjects who receive a specific treatment regimen.

21. (Twice Amended) The method of claim 12, wherein the selected model structures represent structural variants derived from [patients that] subjects who exhibit a particular clinical response to a given drug.

25. A computer-based method of selecting drug therapies for subjects [patients] based on genetic polymorphisms, comprising:

obtaining amino acid sequences of a target protein that is the product of a gene exhibiting genetic polymorphisms, wherein the sequences represent different genetic polymorphisms;

generating 3-D protein structural variant models from the sequences;

computationally docking drug molecules with the target protein models;

energetically refining the docked complexes;

determining the binding interactions between the drug or potential new drug candidate molecules and the models; and

selecting drug therapies based on the drug or drugs that have the most favorable binding interactions with the structural variant models.

27. (Amended) The method of claim 1, further comprising:

after generating the 3-D structural variant models, exporting some or all of them models into a program that computationally docks the models with test compounds to assess intermolecular interactions.

28. (Amended) A computer-based method for predicting clinical responses in [patients] subjects based on genetic polymorphisms, comprising:

obtaining one or more amino acid sequences for a target protein that is the product of a gene exhibiting genetic polymorphisms;

generating 3-D protein structural variant models from the sequences;

building a relational database of protein structural variants derived based on genetic polymorphisms and observed clinical data associated with particular polymorphisms exhibited in the [patients] subjects, wherein the database comprises:

3-D molecular coordinates for the structural variant models;

a molecular graphics interface for 3-D molecular structure visualization;

computer functionality for protein sequence and structural analysis;

database searching tools; and

observed clinical data associated with the genetic polymorphisms, subject medical history and subject history associated with the genetic polymorphisms;

obtaining a target protein structural variant based on the same gene associated with a polymorphism in a [patient] subject;

generating a 3-D protein model based on the subject's gene sequence;

screening/comparing the 3-D model derived from the subject to the structures contained in the database by:

identifying structures in the database that are similar to the model derived from the subject; and

predicting a clinical outcome for the [patient] subject based on the clinical data associated with the identified structures.